REMARKS/ARGUMENTS

Status of the claims

Claims 1-8, 10-13, 22 and 23 are pending and under examination.

Rejection under 35 U.S.C. § 112, second paragraph

The rejection under 35 U.S.C. § 112, second paragraph is withdrawn. However, the Examiner states that the "wherein" clauses in claim 22 step (a) and the second "wherein" clause in claim 1 are intended uses and not assay steps (claim 22) or part of the kit (claim 1). Applicants disagree with the position that the clauses simply recite an intended use. The "wherein" clauses provide elements that are specific characteristics of the lyophilized mixture. These elements are therefore properties possessed by the claimed kits/methods that are relevant to determining patentability of the claims.

The Examiner's statement does not appear to constitute a new rejection under 35 U.S.C. § 112, second paragraph. However, If Applicants' understanding is incorrect and this is a further rejection under this section, it is respectfully requested that this be clearly articulated for the record so that it can be fully addressed on appeal.

Rejection under 35 U.S.C. § 103

Claims 1-8, 13-13, 22 and 23 remain rejected as allegedly obvious over U.S. Patent No. 6,124,110 to Wöber *et al.*; in view of U.S. Patent No. 5,625,036 to Hawkins *et al.*; Váradi *et al.*, *J. Thromb. Haemostasis* 1:2374-2380, 2003 ("Váradi"); U.S. Patent No. 5,952,198 to Chan ("Chan"); U.S. Patent No. 6,074,826 to Hogan *et al.* ("Hogan"); U.S. Patent No. 6,576,422 to Weinstein *et al.* ("Weinstein"); and U.S. Patent No. 6,756,019 to Dubrow *et al.* ("Dubrow"). Applicants have traversed this rejection for reasons of record, which are briefly reiterated below. Applicants' comments in reply to the Examiner's response to the Inventors' Declaration under 37 C.F.R. § 1.132 filed October 21, 2009 begin on page 9 of this paper.

The Examiner has the burden of establishing a *prima facie* case of obviousness. The Supreme Court's ruling in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82

USPQ2d 1385 (2007) emphasized the principles set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) regarding the framework for the objective analysis of obviousness under 35 U.S.C. § 103. The four factual inquires enunciated in *Graham* for determining obviousness include determining the scope and contents of the prior art and ascertaining the differences between the prior art and the claims in issue. As previously explained, the rejection fails to properly determine the scope and content of the prior art in the context of the invention as a whole, and fails to properly ascertain the difference between the claimed invention and the prior art.

In order for an invention to be obvious, the practitioner must also approach the modification anticipating that this modification is going to work in the way that he or she expects. Here, not only does the rejection fail to explain how each element of the invention as a whole is taught or suggested by the prior art or how the prior art can be modified, but there is no evidence presented in the rejection that, prior to Applicants' invention, one of skill would have expected that a lyophilized mixture comprising $CaCl_2$ and a fluorescent thrombin substrate having the characteristics recited in the claims would be soluble in an aqueous solution such as water or plasma.

The rejection does not properly determine the scope and content of the prior art

In brief, the combination of references does not teach or suggest a lyophilized mixture comprising $CaCl_2$ and a thrombin substrate comprising a fluorescent label. As previously explained, Wöber discloses methods of measuring thrombin generation using dried chromogenic substrates, but does not disclose or suggest use of a fluorescent substrate for measuring thrombin generation, much less a lyophilized mixture comprising $CaCl_2$ and the thrombin substrate. Hawkins describes a prothrombin reagent (PT) containing recombinant tissue factor, natural or synthetic phospholipids, calcium ion, and a buffer (*see*, Hawkins, col. 2, line 66 to col. 3, line 1). Hawkins indicates that tissue factor-containing reagents should be stable in a lyophilized state (*see*, col. 1, lines 43-50), but does not disclose or suggest anything regarding the nature of the substrates for a thrombin generation assay. Váradi discloses methods

of measuring thrombin generation using fluorescent substrates, which are provided by the manufacturer as a dried powder and reconstituted in a DMSO-containing buffer (explained in Applicants' response filed January 31 2006), but does not disclose or suggest a lyophilized mixture comprising $CaCl_2$ and a fluorescent thrombin substrate or using such a lyophilized mixture in the methods. All of the aforementioned references are completely devoid of any disclosure or suggestion of a lyophilized mixture comprising $CaCl_2$ and a fluorescent thrombin substrate.

Furthermore, as previously explained, the disclosures of Chan, Hogan, Weinstein, and Dubrow are not relevant to detection of any protein activity, much less thrombin activity: Chan discloses culturing mammalian cells in the presence of a liposome-like substance to increase recombinant Factor VIII production (*see*, abstract); Hogan discloses methods and kits for detecting *Borrelia* nucleic acids and indicates that enzymes, nucleotide triphosphates, primers and probes may be lyophilized (*see*, col. 37, lines 15-17); Weinstein discloses methods of detecting using reporter genes to detect a target of interest (col. 1, line 66 to col. 2, line 17). The methods of Weinstein. may employ a lyophilized "cell or viral detector composition" (*i.e.*, reporter gene) immobilized on a solid support (*see*, col. 16, lines 4-11), but do not suggest a lyophilized mixture comprising $CaCl_2$ and a fluorescent thrombin substrate. Dubrow describes multifluidic devices which may contain a reagent immobilized onto a semi-permeable membrane using lyophilization (col 13, lines 5-6), but does not disclose a lyophilized mixture comprising $CaCl_2$ and a fluorescent thrombin substrate.

There is no hint or suggestion in Wöber or Váradi that the thrombin substrates are lyophilized as a mixture with $CaCl_2$. The substrates and $CaCl_2$ are distinct components of the reactions described in each of these references (*see, e.g.*, Wöber at col. 4, line 47 to col. 5, line 40; Váradi at page 2375, second full paragraph). As explained in the instant specification, addition of $CaCl_2$ to a fluorescent substrate leads to formation of a precipitate (*see, e.g.*, page 9, paragraph 28 to page 10, paragraph 29). Thus, one of skill in the art would not expect that a lyophilized mixture of $CaCl_2$ and a fluorescent substrate could be dissolved in an aqueous solution to form a clear solution.

In addition, dry, powdered substrate is ***not*** a lyophilized substrate. The fluorescent substrates disclosed in Váradi are dried, but not lyophilized. Lyophilization can substantially alter the properties of a starting material. Therefore, one of skill in the art would not be motivated to lyophilize the fluorescent substrates disclosed in Váradi either alone or as a mixture with $CaCl_2$.

None of the other cited references, *i.e.*, Hawkins, Chan, Hogan, Weinstein, or Dubrow, remedy the defects in the combination of Wöber and Váradi because none of the references teach or suggest a lyophilized mixture comprising $CaCl_2$ and a thrombin substrate comprising a fluorescent label or that such a mixture could be dissolved in an aqueous solution to form a clear solution.

No reasonable expectation of success

Moreover, the skilled artisan would have no reasonable expectation of success by combining and modifying the references as suggested by the Examiner. As explained in detail in the instant specification and by Dr. Turecek in his Declaration filed November 3, 2008 as well as Applicants' response dated February 19, 2009, a lyophilized mixture as recited in the claims has the property of being readily soluble in an aqueous solution. The evidence provide by Dr. Turecek further indicates that the DMSO concenteration of the solution prior to lyohilization is not determinative of the increased solubility of such a mixture in water (or plasma or serum). As one of skill in this art, Dr. Turecek additionally attested that the ready solubility of the lyophilized fluorescent substrate/$CaCl_2$ in an aqueous solution was surprising. Without the teachings of the instant specification, the skilled artisan would expect that lyophilization of a fluorescent substrate in the presence of $CaCl_2$ would result in a precipitate when such a lyophilized preparation is reconstituted with an aqueous buffer or water, not the clear solution. Thus, one of skill would not have expected to be able to obtain a lyophilized mixture having the characteristics recited in the claims.

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but

whether the claimed invention as a whole would have been obvious." (MPEP § 2141.02.). The rejection only establishes that various isolated individual elements (fluorogenic thrombin substrates, the existence of a technique to assay thrombin activity, the existence of lyophilization as a process for preparing various compositions) were known in the art, but fails to provide a clear articulation of why these disparate disclosures would lead one of skill to Applicants' invention.

In view of the foregoing, the rejection fails to establish that the claimed invention is obvious. Applicants therefore respectfully request withdrawal of the rejection.

Declaration under 37 C.F.R. § 1.132 filed by inventors

The Examiner also contends that the Declaration under 37 C.F.R. § 1.132 by the inventors (referred to in this section as "the Declaration") that was submitted to remove Váradi as prior art was not sufficient. In particular, the Examiner contends that such a declaration must include concrete supporting evince that inventors who are not authors "could have been authors, i.e., that they contributed intellectually and substantively to the subject matter published in the reference. They provided certain key ideas and explained how the studies to test or prove these ideas should be carried out" (Final Office Action, at page 8). The Examiner further alleges that Applicants cannot submit such a declaration because, according to the Examiner's reasoning, "[A]pplicants have explained in their Declaration that inventors Keil and Peyrer- Heimstaett did not contribute to the subject matter of the reference." Applicants disagree with the Examiner's legal analysis. Applicants also disagree with the Examiner's characterization of the statements in the Declaration regarding the roles of Inventors Keil and Peyrer- Heimstaett as they relate to the cited Váradi publication: the Declaration does not contain a statement that Inventors Keil and Peyrer- Heimstaett did not contribute to the subject matter of the reference.

First, Applicants are not aware of any legal requirement regarding the Examiner's contention that it is necessary to provide notebooks, etc. to establish that Inventors Keil and Peyrer-Heimstaett "could have been authors" on the Váradi publication. Authorship and inventorship are not the same (""[w]e hold that authorship of an article by itself does not raise a

presumption of inventorship with respect to the subject matter disclosed in the article." (*In re Katz* 215 U.S.P.Q. 14, 16). Thus, evidence that could be relevant in determining inventorship is not relevant to whether or not a name appears on a listing of authors of a publication. Further, even assuming solely for argument's sake that the Examiner's position is correct about a requirement to show that Inventors Keil and Peyrer-Heimstaett "could have been authors", this again is not germane to the situation here.

In the previous Office Action dated June 23, 2009, the Examiner stated on page 4 that "...the claimed kit, and the method of its use, appear to be that used by Váradi *et al.* to measure thrombin generation time" (referring to Váradi, p. 2375, right column). Specifically, the Examiner stated that in the assay described by Váradi, "for each assay sample, 10 ul of TF/PL solution is added to 50 ul of a solution containing 1 mM thrombin substrate and 15 mM calcium chloride. 40 ul of plasma is then added to start the reaction" The Examiner then goes on to speculate about how the assay reagent (of Váradi) "could have been made". The Examiner further contends that the quality of solubility in an aqueous solution does not appear to be Applicants' "point of novelty". Although Applicants disagree with the position taken by the Examiner, in view of the Examiner's allegations, Applicants filed the Declaration to attest that to the extent that the invention is disclosed, it is Applicants' invention.

As explained above, Váradi does not teach or suggest the claimed invention. The claims related to kits/methods that employ a lyophilized mixture that has the following property: it is prepared by a process set forth in the claims using a solution comprising the fluorgenic substrate, $CaCl_2$ and DMSO and forms a clear solution when dissolved in water. The dependent claims recite various aspects that involve the TF/PL components. Váradi contains no disclosure relating to, or hinting at, such a lyophilized mixture. The Declaration states "we", *i.e.*, all of the inventors, are inventors of the subject matter of the claims. The Declaration additionally states that to the extent that the invention is disclosed by Váradi, "we" (all of the inventors) are the inventors of that subject matter. The Declaration also states that Inventors Keil and Peyrer-Heimstaett are not named on the Váradi publication because their contribution to the currently claimed invention is not disclosed in the Váradi publication. In the category of invention, their

inventive contribution is in fact not disclosed in Váradi, as Váradi is not relevant to the claims for the various reasons described above. Thus, an analysis of how or why Inventors Keil and Peyrer-Heimstaett may or may not qualify for authorship on the Váradi publication is irrelevant.

Summary

For the reasons explained above, the rejection only establishes that some of the isolated individual elements recited in the claims were known in the art, but fails to provide a clear articulation of why the disparate disclosures describing these elements would lead to Applicants' invention. Moreover, the rejection fails to provide any explanation as to why one of skill would have expected the modifications proposed by the Examiner to result in a lyophilized mixture with the solubility characteristics set forth in the claims.

In view of the foregoing, the rejection fails to establish that the claimed invention is obvious. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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